

method, as determined by the medical history of the donor and from such physical examination and clinical tests as may appear necessary for each donor at the time the blood was obtained. Where source material is a product for which additional standards are effective, the requirements of those additional standards shall determine the propriety of the source material for use in the production of Albumin (Human). Where no additional standards are effective with respect to source material for the production of Albumin (Human), such source material shall:

(1) Be collected by a procedure which is designed to assure the integrity and to minimize the risk of contamination of the source material. The manufacturer of Albumin (Human) shall ensure that the collection procedure shall be as described in its license.

(2) Be identified to relate it accurately to the individual donor and the dates of collection.

(3) Not contain a preservative.

(4) Be stored and transported in a manner designed to prevent contamination by microorganisms, pyrogens, or other impurities.

(c) *Additives in source material.* Source material shall not contain an additive unless it is shown that the processing method yields a final product free of the additive to such extent that the continued safety, purity, potency, and effectiveness of the final product will not be adversely affected.

[42 FR 27582, May 31, 1977, as amended at 50 FR 4140, Jan. 29, 1985]

#### § 640.81 Processing.

(a) *Date of manufacture.* The date of manufacture shall be the date of final sterile filtration of a uniform pool of bulk solution.

(b) *Processing method.* The processing method shall not affect the integrity of the product, and shall have been shown to yield consistently a product which is safe for intravenous injection.

(c) *Microbial contamination.* All processing steps shall be conducted in a manner to minimize the risk of contamination from either microorganisms or other deleterious matter. Preservatives to inhibit growth of microorganisms shall not be used during processing.

(d) *Storage of bulk fraction.* Bulk concentrate to be held more than 1 week prior to further processing shall be stored in clearly identified closed vessels at a temperature of  $-5^{\circ}\text{C}$  or colder. Any other bulk form of the product, exclusive of the sterile bulk solution, to be held more than 1 week prior to further processing shall be stored in clearly identified closed vessels at a temperature of  $5^{\circ}\text{C}$  or colder. Any bulk fraction to be held one week or less prior to further processing shall be stored in clearly identified closed vessels at a temperature of  $5^{\circ}\text{C}$  or colder.

(e) *Heat treatment.* Heating of the final containers of Albumin (Human) shall begin within 24 hours after completion of filling. Heat treatment shall be conducted so that the solution is heated for not less than 10 or more than 11 hours at an attained temperature of  $60^{\circ}\pm 0.5^{\circ}\text{C}$ .

(f) *Stabilizer.* Either 0.16 millimole sodium acetyltryptophanate, or 0.08 millimole sodium acetyltryptophanate and 0.08 millimole sodium caprylate shall be added per gram of albumin as a stabilizer.

(g) *Incubation.* All final containers of Albumin (Human) shall be incubated at  $20$  to  $35^{\circ}\text{C}$  for at least 14 days following the heat treatment prescribed in paragraph (e) of this section. At the end of this incubation period, each final container shall be examined and all containers showing any indication of turbidity or microbial contamination shall not be issued. The contents of turbid final containers shall be examined microscopically and tested for sterility. If growth occurs, organisms shall be identified as to genus, and the material from such containers shall not be used for further manufacturing.

[42 FR 27582, May 31, 1977, as amended at 50 FR 4140, Jan. 29, 1985]

#### § 640.82 Tests on final product.

Tests shall be performed on the final product to determine that it meets the following standards:

(a) *Protein content.* Final product shall conform to one of the following concentrations:  $4.0\pm 0.25$  percent;  $5.0\pm 0.30$  percent;  $20.0\pm 1.2$  percent; and  $25.0\pm 1.5$  percent solution of protein.

(b) *Protein composition.* At least 96 percent of the total protein in the final

product shall be albumin, as determined by a method that has been approved for each manufacturer by the Director, Center for Biologics Evaluation and Research, Food and Drug Administration.

(c) *Hydrogen ion concentration.* The pH shall be  $6.9 \pm 0.5$  when measured in a solution of the final product diluted to a concentration of 1 percent protein with 0.15 molar sodium chloride.

(d) *Sodium content.* The sodium content of the final product shall be 130 to 160 milliequivalents per liter.

(e) *Heme content.* The absorbance at 403 nanometers of a solution of the final product diluted to a concentration of 1 percent protein in a cell with a 1-centimeter light path shall not exceed 0.25.

(f) *Heat stability.* A final container sample of Albumin (Human) shall remain unchanged, as determined by visual inspection, after heating at 57 °C for 50 hours, when compared to its control consisting of a sample, from the same lot, which has not undergone this heating.

[42 FR 27582, May 31, 1977, as amended at 49 FR 23834, June 8, 1984; 50 FR 4140, Jan. 29, 1985; 55 FR 11013, Mar. 26, 1990]

#### § 640.83 General requirements.

(a) *Preservative.* The final product shall not contain a preservative.

(b) *Storage of bulk solution.* After all processing steps have been completed, the sterile bulk solution shall be stored in a manner that will ensure the continued sterility of the product, and at a temperature that shall not exceed the recommended storage temperature of the final product prescribed in § 610.53 of this chapter.

[42 FR 27582, May 31, 1977]

#### § 640.84 Labeling.

In addition to the labeling requirements of §§ 610.60, 610.61, and 610.62 of this chapter,

(a) The container and package labels shall contain the following information:

(1) The osmotic equivalent in terms of plasma, and the sodium content in terms of a value or a range in milliequivalents per liter;

(2) The cautionary statement placed in a prominent position on the label, "Do Not Use if Turbid. Do Not Begin Administration More Than 4 Hours After the Container Has Been Entered.";

(3) The need for additional fluids when 20 percent or 25 percent albumin is administered to a patient with marked dehydration;

(4) The protein content, expressed as a 4 percent, 5 percent, 20 percent, or 25 percent solution.

(b) The type of source material, expressed as venous plasma, placental plasma, or both, used to manufacture the final product shall appear on either the container or package label or in the package insert.

[42 FR 27582, May 31, 1977, as amended at 49 FR 2244, Jan. 19, 1984]

### Subpart I—Plasma Protein Fraction (Human)

SOURCE: 42 FR 27583, May 31, 1977, unless otherwise noted.

#### § 640.90 Plasma Protein Fraction (Human).

(a) *Proper name and definition.* The proper name of the product shall be Plasma Protein Fraction (Human). The product is defined as a sterile solution of protein composed of albumin and globulin, derived from human blood.

(b) *Source material.* The source material of Plasma Protein Fraction (Human) shall be blood, plasma, or serum from human donors determined at the time of donation to have been free from disease-causative agents that are not destroyed or removed by the processing method, as determined by the medical history of the donor and from such physical examination and clinical tests as may appear necessary for each donor at the time the blood was obtained. When source material is a product for which additional standards are effective, the requirements of those additional standards shall determine the propriety of the material for use in the production of Plasma Protein Fraction (Human). When no additional standards are effective with respect to source material for the production of Plasma Protein Fraction (Human), such source material shall: